April 29, 2002

Dr. David M. Burns
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Dear Dave:

Thanks for sending me a copy of Monograph 13. I, and some of our scientists, have given it a lot of thought.

Regarding the cigarette design alternatives that have been developed for smokers, I agree that these have predominantly made use of technologies, such as ventilation and expanded tobacco, with the objective of affecting the amount of smoke delivered, not the relative quality or biological activity of the smoke delivered (as was stated in your monograph). I must add that I am a little confused because it seems that there are conflicting statements in different parts of the monograph regarding whether or not there were changes in the relative quality of the smoke.

Regarding actual smoke exposure of smokers, we agree that a degree of compensation occurs and the frequency and extent must be accounted for. Also, I get the sense we agree that the literature is not sufficiently clear on the magnitude of the compensation such that a definitive statement can be made, if I can judge that by the qualified wording of statements from chapter 1: low tar cigarettes "did not substantially lower exposure", there is "little reason to expect" decreased risk from switching to low tar products, and "there appears to be complete compensation". The methods used to measure exposure and their application, both direct and indirect, had and still have limitations. To address this, as you know, we have started a large scale exposure study that is designed to quantify the total smoke exposure of U.S. smokers of manufactured cigarettes, as well as provide quantitative information for characterizing smoke exposure *vs* FTC delivery to an extent that has been not done to date, a question at the heart of Monograph 13. Besides sharing our study design with you in 2000, we have shared it with many other interested parties in the field and have presented the design at several domestic and international scientific conferences. The pilot study that was initiated to determine the feasibility of the approach and the sample size required has completed its clinical phase and is currently under evaluation. The first data has just been presented at the SRNT Conference in Savannah, Georgia, in February.

Your report has also stated that the "most important question on compensatory smoking is the extent to which it occurs when smokers actually switch brands of cigarettes through their own choice. Unfortunately this is the most difficult circumstance under which to obtain detailed measurements of large numbers of smokers." We appreciate that concern and are adding this as a follow-up study to the large exposure study, as per your recommendation after the presentation of this study design at the meeting convened by Greg Connolly in Massachusetts in 2000.

Regarding disease risks, we agree that epidemiological studies show a relationship between low tar cigarette use and decreased lung cancer. This relationship is a small one (relative reduction of risk of less than 50%), but it does have consistency, dose-response, and biological plausibility. We are not convinced, from some analysis we have done and would be happy to share and discuss, that this result is changed by evaluation of cigarettes per day.

Although we also agree that the decline in lung cancer death rates in the US through 1990 can be fully accounted for by the decline in smoking prevalence, at a time when tar deliveries were decreasing, it appears that looking at lung cancer death rates beyond 1990 shows a decrease in cancer rates greater than predicted by smoking incidence. As you mention, the UK also shows a decrease in cancer rates, which is greater than the decreased smoking prevalence would predict.

We further agree that the comparison of the two large prospective mortality studies (CPS I and CPS II) show an increase in the risk of lung cancer from smoking while machine-derived tar and nicotine yields were decreasing. As you stated, you cannot eliminate the increase in risk by adjusting for cigarettes per day or for duration of smoking. Of course, it would be important to know why. Thun and Health, in 1997, suggest considerations such as demographics, starting age of smoking, or cigarette hazard increase. They also ask the question, might the increase have been worse but for the low tar designs? To that point, you still see a decrease in cancer risk in CPS I and CPS II, adjusted or unadjusted for cigarettes per day, between high tar and low tar smokers.

In the end, there are some clear results, and some conflicting results. You raise some good questions for further study, and I would even add some. As you say, what is the cancer risk for smokers of only low and ultra-low tar cigarettes? In fact, the current studies address only down to 10 mg tar. Not only should the UK smokers who currently show a decrease in cancer rates be followed as you suggest, but don't overlook following the US population further. Certainly we agree that evaluation of the numerous new product designs proposed to reduced exposure or risk should be evaluated, and we are pursuing this as well as other relevant knowledge gaps. In that context, the affect on initiation and cessation is an important factor in the responsible implementation of harm

reduction. Is there research planned in the public health community to fill some of these gaps as well?

One of my concerns at present, which stems from the lack of clarity as to whether there is even a minimal benefit from low tar cigarettes, is the following: What if, based on Monograph 13, consumers believe there is no difference, and there is a subsequent large switch to full flavor cigarettes, is there enough confidence in the data to be assured that an increase in disease will not result? Even if the degree of exposure reduction is too small to meet the criteria defined by the IOM in "Clearing the Smoke" for an exposure reduction claim, how sure are we that the machine derived delivery numbers are not at least directionally correct, and thereby have some impact on harm? That's not to say that such an impact would be a replacement for the best way to reduce the harm of smoking, which is to quit. Hopefully we will all conduct any necessary further analysis expeditiously to allow real progress.

Thanks for the offer to discuss this. We would like to take you up on it. There is plenty to discuss, even just in this monograph, and these are only brief comments. I'll call you after you've had a chance to digest this letter.

In the interest of pursuing more open communication, I've also copied this letter to Neal Benowitz since you were the two scientific editors, and to Scott Leischow since the report was an NCI monograph. Please don't hesitate to share this with other scientists if you think it might help stimulate dialogue and move these efforts forward.

I look forward to talking with you about this.

Sincerely,

cc: Neal Benowitz, UCSF
Scott Leischow, NCI